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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/235,986	01/22/1999	WAYNE A. HENDRICKSON	58323/JPW/PT	2152

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JOHN P WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF AMERICAS
NEW YORK, NY 10036

EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 04/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/235,986	HENDRICKSON ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 7/28/03 (arguments and Teng Declaration) and 1/26/04 (claims in proper format) have been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-12 are under consideration by the examiner.

Claim Rejections - 35 USC § 112

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1 and 7 have been substantively amended. Applicant has not pointed to any basis for these changes and none is apparent. It is noted that the present form of claims 1-12 bears limited resemblance to original claims 1-12. Applicant must point out by page and line number

the basis for each step (individually and as being part of the recited process steps collectively) in support of the system and process as now claimed. The limitations set forth in the instant claims don't match those of the original claims in a broad sense or in particulars. Failure to point to basis in applicant's next response will be considered non-responsive.

Claim Rejections - 35 USC § 112

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some aspects of the claimed method and system, does not reasonably provide enablement for the breadth of what is encompassed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-6 are directed to a system comprising a database, at least one bioinformatics tool, a protein synthesis means having a screening means, a protein processing means, a crystallization means, an X-ray crystallography means, a structure extraction means, and a homology model building tool. The prior Office action sets forth the reasons that an integrated, turn-key system or fully automated system is not enabled. Applicant's response essentially concedes that such a system is not enabled and argues that the unintegrated system is enabled. As such, claims 1-6 embrace an integrated system that is not enabled.

In addition, the system of claims 1-6 encompasses a synchrotron. (See in particular claim 4.) The prior Office action sets forth the reasons that a system including this apparatus as well as a method using this apparatus are not enabled. Applicant argues on page 13 of the response that a number of publicly accessible facilities that include synchrotrons with undulator beams exist. This is not agreed with. Beamline time must be applied for at existing synchrotron facilities.

Many requests for use are turned down due to lack of facilities. Applicant has not established that synchrotrons would have been readily available and accessible to those wishing to practice the claimed invention. While applicant argues there is no bar against the patenting of inventions that are costly to practice, the examiner maintains that as set forth in the prior Office action, synchrotrons cost approximately $100,000,000.00, take approximately 10 years to build, and can't be purchased from a catalog. This is not so much costly as prohibitive to those wishing to practice the invention. To the best of the examiner's knowledge, the inventors themselves are not in possession of a synchrotron but must also arrange to use existing facilities to practice the claimed method.

With respect to claims 7-12, the claimed method fails to particularly point out what steps are to be performed and how they are to be performed. For example, claim 7 recites "using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database." This does not illuminate which bioinformatic tool, what specific information, or how to use it to achieve the goal of clustering. It does not provide the positive, active steps to perform on unspecified structural or sequence information to arrive at a plurality of families within the context of the claims. For example, the database has sequence information for a first plurality of proteins and structural information and functional information for a second plurality of proteins. (Note that it is unclear if this is a partitioned database for the first and second plurality as they do not contain the same types of information.) For example, say the structural information for the second plurality is polymeric structure (monomer, dimer, etc.). For example, say the functional information for the second plurality is enzymatic activity (protease, synthase, etc.) How does one practicing the invention use polymeric structure and

enzymatic activity to cluster into a plurality of families? For example, proteins A, B, and C are in the first plurality and proteins D, E, and F are in the second plurality. Protein D is a monomeric protease. Protein E is a trimeric synthase. Protein F is a monomeric protease. What is the plurality of families that the at least one bioinformatics tool identifies? How are homologous sequences for the family determined if the database does not contain sequence information for D, E, and F and their sequences cannot be compared to sequence information for A, B, and C? The specification provides no discussion or guidance for adapting bioinformatics tools to make such determinations. Going further in the claim to step (g), the refined model is stored in the database. Note that part (a) does not require that the structural information include a refined model or a homology model. Going further in the claim to step (j), the database is updated to link the refined model to other databases. Note that part (a) does not require that the database have links to any information at all. The method steps as written are internally inconsistent. As written, one of ordinary skill in the art would be unable to practice the method for at least these reasons.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 7 recite "homologous sequences." However, it is unclear what level of homology is required to meet the limitation of the claims.

Claims 1 and 7 recite "a plurality of target proteins which are members of the family." However, the criteria that define a family are not provided. It is unclear how a target is selected (what parameters or criteria are used) and how many targets are selected.

Applicant argues that various known programs can be used and that one of ordinary skill in the art would not find these two phrases unambiguous. This is unpersuasive. The claims and specification must particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant has not provided an art understood meaning for these phrases either within the specification or using art recognized documentation.

Claims 1 and 7 have been amended to recite "which are effective as the target proteins." I t is not known what is meant by this phrase. What defines an effective target protein?

Claims 1 and 7 have been amended to recite "screening products of the synthesis to choose selected synthesized products for processing." However, the criteria or parameters for the selection are not provided.

With respect to claims 1-6, the claimed system does not set forth the relationship of the database, bioinformatics tool, protein synthesis means, protein processing means, crystallization means, X-ray crystallography means, and so forth. That is, the claim language does not reflect an integrated or turn-key system where the components are related or linked to each other in some fashion. As written, the claim appears to be directed to a collection of laboratory equipment or machines. A collection of laboratory equipment or machines does not define a system. Applicant's response on page 18 indicates that the claim is not limited to a turn-key system. See art rejection below.

With respect to claims 7-12, the method steps as written are internally inconsistent and unclear. For example, in step (a) the database has sequence information for a first plurality of proteins and structural information and functional information for a second plurality of proteins. (Note that it is unclear if this is a partitioned database for the first and second plurality as they do not contain the same types of information.) In step (g), the refined model is stored in the database. Note that part (a) does not require that the structural information include a refined model or a homology model. In step (j), the database is updated to link the refined model to other databases. Note that part (a) does not require that the database have links to any information at all.

Claim Rejections - 35 USC § 102

Claims 1-12 are rejected under 35 U.S.C. 102(a) as being anticipated because the invention was known by others in this country before the invention thereof by applicant for a patent as evidenced by the Workshop on Structural Genomics held at Argonne National Laboratories held January 1998, National Institute of General Medical Sciences (NIGMS) Protein Structure Initiative (PSI) held 4/24/98, NIGMS Genomics Project Planning Meeting held 11/24/98, Structural Genomics Meeting held October 1998 in Avalon, New Jersey, Shapiro et al. (Current Biology, 15 March 1998) and Gaasterland (Nature Biotechnology, July 1998).

The prior Office action rejected claims 1-12 under 102(a) as being anticipated by the National Institute of General Medical Sciences (NIGMS) Protein Structure Initiative (PSI) Meeting Summary dated 4/24/98. This document summarizes the discussion of a one-day meeting held on 24 April 1998 to experimentally determine 3D structures of protein families via

a representative protein molecule (target) from each family. Protein sequences were compared using sequence homology to define families and targets selected. The targets are then cloned into plasmids for overexpression, and purified for use in crystallization trials. Those targets successfully crystallized have X-ray crystallography and protein structure determination performed. Synchrotrons, multiwavelenth anomalous diffraction (MAD), and selenomethionyl enrichment are specifically disclosed. Structural and functional properties would be predicted. In particular, identification of protein fold motifs is disclosed. The results of the analysis are put in a database with any additional information that may be helpful for further experiments. The database is updated and annotated as research progresses. The database is intended to be accessible to all researchers. (See in particular pages 4-15 of document.) Implicit in this document is a system containing the component parts (database and means) for executing each of the steps of the method.

Applicant submitted the Teng Declaration and argues that this publication is not prior art. It is noted that applicant concedes an availability date of May 12, 1999 for this material as a publication. Applicant argues that the content of any prior version cannot be verified. Applicant is advised that Exhibits 2 and 3 of the Teng Declaration appear to be identical. Neither exhibit lists the modification dates referred to in Exhibit 1. Clarification is requested.

However, 35 USC 102(a) is not limited to description in a printed publication before the invention thereof by the applicant for patent. It includes whether the invention was **known** by others in this country before the invention thereof by the applicant for a patent. The fact that this meeting (as well as the other meetings cited above and publications discussing the meetings cited above) took place or were published prior to applicant's filing date indicates that the invention

was known. Applicant has not presented evidence disputing the content of what was discussed at these meetings. Applicant has submitted Exhibits 1-10 on 9/30/02. The draft agenda, letters, slides from oral presentations, Hendrickson's notes, etc. are all consistent with the meeting summaries. In particular, Hendrickson's notes from Chris Sander's talk include comments on homology modeling, deriving families, and picking a 3D target from each family (see page 1). His notes from Paul Godowski's talk include comments on going from cDNA to crude protein to pure protein to crystals (including assaying for quality crystals) to structure (see page 4). His notes from Janet Thornton's talk include comments about basic data, family sequence and structure information, functional motifs in 3D, ligand binding sites and linking this information to functional information, pathway information, expression and genome data (see page 10).

The summary of the NIGMS Structural Genomics Project Planning Meeting (11/24/98) indicates that the various experimental components of the structural genomics project were summarized, especially the high-throughput method. The computational tasks of protein classification and target selection under way in various laboratories was discussed. The expected benefits were discussed. (See pages 1-4 of 8.)

Shapiro et al. also summarizes the Argonne Structural Genomics Workshop in a meeting review. The goal of building a comprehensive structural database using large-scale structure determination X-ray crystallography (including crystal freezing and MAD phasing and third generation synchrotrons having undulator beamlines) is disclosed. A class based approach using sequences and determination of the structure of a representative number from each and every class is disclosed. (See also Kim, Nature Structural Biology, Synchrotron Supplement, August

1998, who was present at the meeting and whose work is discussed by both Shapiro et al. and Gaasterland.)

As set forth in the prior Office action, Gaasterland reviews the goals and initial results of the structural genomics initiative. Results from the pilot project presented in January 1998 at the Argonne National Laboratory are discussed. Flow diagrams (Figures 1 and 2) and particular bioinformatics tools (Table 1) with the accompanying discussion are considered to disclose the claimed methods and system. Gaasterland discloses genome analysis and target selection. The genome information disclosed is clearly in the context of an annotated sequence database. Cross-genome comparisons would clearly indicate clustering and homologous sequence analysis to one of ordinary skill in the art, particularly where selection of targets is discussed. See for example page 626, rightmost column, "1000-3000 folds as a lower limit, and five dissimilar sequence clusters per fold" and "computational comparison subsets of proteins from multiple whole genomes provided critical data for selecting targets for new folds." It is noted that Gaasterland specifically discusses the Protein Data Bank (PDB) (see at least Figures 1 and 2) which would have been known at the time of the invention to contain information including atomic coordinates, bibliographic citations, primary and secondary structure information, crystallization structure factors. This includes pointers to other databases which contain a variety of additional information. The PDB would have been internet accessible. (See Sussman et al., Acta Chyrstallographica Section D, 1998). Gaasterland specifically references the

With respect to the system of claims 1-6, applicant has conceded that the named components are not required to be linked in any particular fashion as a turn-key system. These claims do not require that the output from means must be in a form to act directly, automatically,

seamlessly, or otherwise, as input for the next means. As such, each of these discrete components (a database with sequence, structural, and functional information; at least one bioinformatics tool capable of clustering; protein synthesis means with screening means; protein processing means; crystallization means; X-ray crystallography means; structure extraction means able to build a refined model; and a homology building tool) having the functionality required by the claims, would have been discussed at these various meetings and thus the system as claimed would have been known.

The documents of record pertaining to the cited meetings provide every indication that the claimed system and method were discussed in a general way and a particular way with respect to particular methodologies to practice the method to those in attendance. The structural genomics problem was the whole point of these meetings. The flow chart of Gaasterland and knowledge of skill in the art on the various techniques would have enabled one to practice the invention. Should applicant argue otherwise, they are inviting an enablement rejection with respect to their methods for the same reasons. Finally, it is noted that Gaasterland was both an organizer and a presenter at the January meeting.

Claims 1-12 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter in view of the Workshop on Structural Genomics held at Argonne National Laboratories held January 1998, National Institute of General Medical Sciences (NIGMS) Protein Structure Initiative (PSI) held 4/24/98, NIGMS Genomics Project Planning Meeting held 11/24/98, Structural Genomics Meeting held October 1998 in Avalon, New Jersey, and Gaasterland (Nature Biotechnology, July 1998).

While at least inventor Hendrickson is indicated to have been present at some of the meetings, the claimed invention in its totality appears to have been conceived of by a multiplicity of people and not just Hendrickson and Honig.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Thursday, 5:30 am - 1:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne P. Allen 4/22/04
Marianne P. Allen
Primary Examiner
Art Unit 1631

mpa